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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE

Office Action Summary

Application No.	Applicant(s)
09/096,648	Hadlaczky & Szalay
Examiner	**Group Art Unit**
Jill D. Martin	1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-63* is/are pending in the application.

Of the above, claim(s) *1-31, 45-58, and 61-63* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *32-44, 59, and 60* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-31, 45, 48-56, 61-63, drawn to artificial chromosomes, methods of making them, vectors comprising them, cells and cell lines comprising them, methods of expressing genes in them and a method of using them to clone centromeres, classified in class 526, subclass 23.1, and class 435, subclasses 69.1, 91.4, 240.2, 320.1.

II. Claims 32-42, drawn to a transgenic animal and method of making it, classified in class 800, subclass 2.

III. Claims 46-47, drawn to a method of making a transgenic plant, classified in class 800, subclass 2.

IV. Claims 57-58, drawn to a method of gene therapy, classified in class 435, subclass 172.3.

Claims 43-44, 59, and 60, drawn to methods of making transgenic animals or plants, classified in class 800, subclass 2 link inventions II and III. Upon election of either Group II or III, these claims will be examined to the extent that they read on the elected invention. These claims are improper genus claims because they encompass non-equivalent, patentably distinct inventions (transgenic animals and

transgenic plants). A suitable amendment is required so that upon election, the claims read on the elected invention only.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II, III and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the compositions and methods of Group I are patently distinct from the compositions and methods of Groups II, III and IV because the artificial chromosomes of Group I can be used in the materially different processes of Groups II, III and IV.

The gene therapy method of Group IV is patently distinct from the transgenic animals and plants of Groups II and III, because the gene therapy methods require a search of methods of introducing therapeutic agents into, and analyzing their effects on, whole organisms, and such areas of search and consideration are not required for analysis of transgenic animals and plants. The transgenic animals of Group II are derived from materially different cell types than the transgenic plants of Group III, which e.g. contain cell walls that are absent in the animal cells of Group II. The required searches for groups I-IV are therefore non-coextensive.

Because these inventions are distinct for the reasons given above, have acquired a separate status in the art as shown by their different classification, require con-coextensive searches in both

the patent and non-patent literature, and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Paula Schoeneck on August 5, 1999 a provisional election was made without traverse to prosecute the invention of Group II, claims 32-44, 59, and 60, in so far as the claimed invention is drawn to transgenic animals and not transgenic plants. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-31, 45-58, and 61-63 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claim 42 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 42 is directed to a transgenic animal, the scope of which encompasses a human being. A human being is non-statutory subject matter. As such, the recitation of the limitation "non-human" would be remedial. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-44, 59 and 60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is drawn to methods of making transgenic animals by means of mammalian artificial chromosomes (MACs), specifically satellite artificial chromosomes (SATACs) (claims 32-41) or minichromosomes (claims 43-44, 59, and 60), and to a transgenic animal made by these methods (claim 42). The production of transgenic animals by such methods is not well-established in the art; in the absence of guidance in the art as to how to make and use MACs in this manner, the artisan must rely on the specification, and the specification does not

teach how to make or use transgenic animals by these methods. In particular, although the specification teaches how to generate specific SATACs or minichromosomes, it does not teach how to generate MACs that contain and express heterologous genes, how to introduce MACs into embryos or ES cells, or how to generate transgenic animals which express heterologous genes at a high enough level to be useful. Each of these concerns will be considered in turn.

The specification discloses that MACs can be useful for producing transgenic animals expressing a gene(s) of interest. The specification discusses that introduction of the MAC comprising the gene of interest into an embryonic stem cell or embryo would provide a means for producing a disease-resistant transgenic animal, for example. See page 40, lines 14-16.

As a first issue, the specification fails to teach or provide guidance for the production of a transgenic animal, including a transgenic mouse, whose genome comprises a MAC which exhibits proper chromosome behavior such that a transgene(s) would be expressed. For example, Jiewen et al. (Theriogenology, 1996) disclose that proper MAC behavior or viability of a MAC in a host is measured by its proper decondensation, replication, and segregation into the daughter blastomeres along with embryo cleavage and proper expression of the transgenes. In fact, Jiewen et al. conclude that proper decondensation is essential for DNA replication. However, the specification fails to teach or measure any of these critical parameters. As such, the specification fails to teach the production of transgenic animals carrying viable MACs and expressing heterologous genes. Furthermore, Jiewen et al. teaches that chromosome transgenics must

involve microcell fusion which is not taught in the description of the production of the transgenic animals in the specification.

It appears from a careful reading of the specification and of a post-filing published paper reporting some of these results [Kereso *et al* (1996) (JH)] that a few stable chromosome variants were obtained as rare occurrences during the manipulation and culture of cell line EC3/7C5 (which comprises a dicentric chromosome) and of its derivatives. The additional centromere in the dicentric chromosome in EC3/7C5 originated from human chromosome 7. From EC3/7C5 were obtained the neo-minichromosome disclosed previously in US Pat. No. 5,288,625 (1994) (BH) (Hadlaczky) and a "sausage" chromosome (that occurred once in the 62 lines analyzed). A cell line comprising the "sausage chromosome" was fused to CHO cells and subcultured under various conditions, and gave rise to a gigachromosome (once in 27 cell lines analyzed) and to megachromosomes of various sizes. The "sausage" chromosome, gigachromosome and megachromosomes are all subsumed under the name SATAC, or satellite artificial chromosome, since all are "stable heterochromatic chromosomes...made primarily of repeating units of short satellite DNA and are fully heterochromatic" (as described in the specification e.g. at p. 4, lines 12-15 and p. 6, lines 1-3). There is no indication in the specification that these forms of MACS could be obtained in a reproducible fashion. Although the specification discloses that a dicentric chromosome can also be generated from human chromosome 1, there is no indication that this dicentric chromosome can give rise to stable derivative MACs. There is no indication in the specification that centromere amplification can occur in other mammalian chromosomes, and

there is certainly no indication that the phenomenon can occur in centromeres from other species, such as fish, insects, amphibians or arachnids (as recited in claim 40). Given the lack of understanding of the structure and function of centromeres, coupled with the rare occurrence of the MACs, the only MACs, minichromosomes or SATACs whose derivation is enabled are those which are exemplified in the specification and which have been deposited.

Even if it is acknowledged that the specific artificial chromosomes described in the preceding paragraph as being enabled can be made, there is no evidence that they can be used as a basis for introducing and expressing foreign heterologous genes in animals. Of the disclosed MACs, only the sausage chromosome in TF1004G-19 was shown to express a foreign sequence, β-gal. The expression was identified by *in situ* hybridization but was not quantified. Even if it could be shown that this MAC could be introduced into transgenic animals and expressed in them at a high level, it is not clear how such an animal would be used, because the specification does not disclose a use for an animal whose cells express β-galactosidase. The actual intended use of the disclosed MACs appears to be to serve as the basis for expressing heterologous genes, such as CFTR or a sequence encoding an anti-HIV-tat ribozyme. The specification teaches that one could introduce such sequences into MACs by *in vivo* homologous recombination into sequences present in the MACs such as phage λ sequences. However, the art suggests that such homologous recombination would occur rarely, if at all, and the specification does not provide guidance as to how to accomplish such integration.

It is unpredictable whether heterologous DNA could be inserted into MACS by *in vivo* homologous recombination. Brown *et al* (1996) (ET) point out (see e.g. section beginning on p. 282, final paragraph, and continuing to p. 283) that the frequency of recombination in mammalian somatic cells is too low to allow for such manipulation, and that MACs would have to be shuttled into alternative cellular hosts. However, they note that yeast cells would not be suitable hosts because tandemly repeated sequences such as those found in centromeres are unstable in this system; yeast cannot handle DNA much larger than its largest chromosome (~2.5 Mb); and transformation of yeast with DNA molecules larger than ~1 Mb is very inefficient. Furthermore, they note that mouse ES cells, which have higher rates of homologous recombination than somatic cells, are probably not suitable hosts either, because the rate of homologous recombination can be very low at particular loci, so it would require extensive experimentation to determine if a given homologous recombination event could occur. Brown *et al* (ET) suggest that one might be able to accomplish the desired homologous recombination in a background of certain avian cell lines, but it has not been demonstrated in the art or in the specification that such recombination could occur with MACs, and the fact that the transfer of SATACs into CHO cells resulted in major alterations in the structure of some SATACs suggests that the fate of SATACs introduced into avian cells would be unpredictable.

Even if Applicant could show that heterologous DNA could be inserted into a MAC, it is unpredictable whether the inserted DNA would be expressed, particularly in view of the fact that the inserted sequences would be imbedded within heterochromatic sequences. The current dogma

is that centromeric sequences, and heterochromatic DNA in general, silence the expression of adjacent genes (see e.g. Henikoff (1990) (IK), p. 422, paragraphs 2 and 3). Although Applicant discloses one instance in which a heterologous gene located near such heterochromatic sequences is expressed (β-gal in TF1004G-19), that finding was surprising, and an artisan would require evidence that the phenomenon is indeed reproducible. Furthermore, the specification does not quantitate the level of expression of β-gal in those cells. In order for an artisan to know how to use a transgenic animal, the animal must express a heterologous protein at a high enough level to give rise to a phenotype; therefore, a method of producing transgenic animals must insure that the animals will indeed be able to express heterologous sequences efficiently. The specification does not teach that heterologous sequences can be expressed efficiently either *in vitro* or *in vivo*, and the art suggests that such expression would not occur.

As a second issue, the claimed invention is directed to transgenic mammals and methodology employing ES cells. However, the prior and post-filing art are replete with references which indicate that ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See also Moreadith et al. (J. Mol. Med., 1997), page 214, Summary. In addition, Seamark (Reproductive Fertility and Development, 1994) discloses that totipotency for ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Mullins et al. (Journal of Clinical Investigation, 1996) disclose that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been

successfully demonstrated." (page S38, column 1, first paragraph). As the certain of the claims require introduction of the MAC into an ES cell, the state of the art supports that only mouse ES cells were available for use for production of transgenics.

To this regard, the specification (and claim 41) broadly suggest a number of methods by which one could introduce MACs into embryos or ES cells, it does not exemplify any such transfer, and the art suggests that such large molecules could not be efficiently introduced. Several of the proposed methods will be discussed below. Note that the specification suggests the introduction of large genes such as CFTR (~230 kb), and that the disclosed SATACs are ~100-150 Mb ("sausage chromosome"), ~250-400 Mb (megachromosomes) or >1000 Mb (gigachromosome). Lamb *et al* (1995) (JO) teach that although YACs as large as 250 kb have been introduced into mouse embryos by microinjection, the efficiency is generally only one tenth that observed when smaller plasmid or cosmid DNAs are introduced, and that the artisan faces problems of shearing and fragmentation of the DNA during microinjection (see e.g. p. 344, col. 1); one would expect to encounter even greater difficulties with MACs. Lamb *et al* also teach that although YACs as large as 650 kb have been transfected into ES cells by lipofection, the artisan faces problems of DNA fragmentation during isolation and transfection (see e.g. p. 343, col. 1); again, one would expect to encounter even greater difficulties with MACs. Huxley (1994) (IT) teaches (see e.g. section entitled "Delivery", beginning on p. 8, col. 2) that viral methods of delivery are limited to inserts of ~10 kb for retroviruses to ~150 kb for HSV-1, and that particle bombardment is likely to shear large DNA molecules. It is unpredictable whether

large MACs could be delivered into embryo or ES cells by any method, and the specification does not exemplify the successful delivery of such a DNA molecule or provide guidance as to how to do so.

Furthermore, Huxley (IT) cautions that "a more severe problem" might be the preparation of milligram amounts of the large DNA. Note that, in order to deliver molar amounts of a gene comparable to those delivered by smaller vectors, one must deliver considerably larger milligram amounts of a large vector such as a MAC. In addition to the problems of purifying such DNA in an intact form, the artisan would be faced with problems of viscosity and the need to deliver extremely high amounts of foreign, potentially toxic, DNA, to the recipient embryo cell. The specification provides no guidance as to how much DNA would be required to generate a transgenic animal, and whether the necessary amount could be purified and delivered.

As a final issue, the specification does not teach whether MACs would be maintained stably in transgenic animals. Although some of the MAC forms are shown to be stably maintained in mouse or hamster cells for as long as 100 cell divisions *in vitro*, it is not clear whether MACs would be so maintained under *in vivo* conditions, or whether MACs bearing inserts of large DNAs would be maintained stably, and in an unarranged form, either *in vitro* or *in vivo*. Given the degree to which cultured EC3/7C5 cells give rise to modified forms of MACs, it is not predictable what modifications would occur *in vivo*, and how that would affect the stability of the DNA and the expression of genes therein. Furthermore, it is not predictable whether MACs whose centromeres are of human or mouse origin (as in the exemplified MACs) would function in

other species. Claim 40 suggests that SATACs could be used to generate transgenic fish, insects, reptiles, amphibians, arachnids, or unspecified mammals. However, given how little is understood about the structure and function of centromeres from any species, including human and mouse, an artisan could not predict whether MACs bearing centromeres from mouse or human would function in those organisms. For example, would the MACs distribute properly to daughter cells during cell division during the development of the organism? Also, would the apparent origin of replication that is located within these centromere sequences function in a heterologous species?

It is also not clear whether MACs could be maintained in the germline. Brown *et al.* (ET) point out that male meioses are particularly sensitive to the presence of unpaired chromosomes, and that an unpaired marker chromosome will often block male meiosis during the first division. He discusses several approaches to get around this sort of problem, but cautions that it is unclear whether they will work (see e.g. p. 287, col. 1, lines 1-27).

Furthermore, without evidence to the contrary, it is noted that, generally, transgene behavior cannot be extrapolated from one species of animal to another. For example, Wall (Theriogenology, 1996) discloses the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements and may result in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Kappel et al. (JE) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, 3rd full paragraph). Strojek and Wagner (NF) pointed out that a high degree of expression of a transgene in a mouse

is often not predictive of high expression in other species, including pigs and rabbits, because, for example, the cis acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 238-239). Given such species differences in the expression of a transgene, it would have required undue experimentation to extend the results achieved in transgenic mice to the levels of transgene product in any other transgenic animal, the consequences of that production, and therefore, the resulting phenotype. Mullins et al. (Journal of Clinical Investigation) support this observation by stating that "[t]he use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." (page S39, Summary).

Claim 42 is broadly drawn to a transgenic animal generated with a MAC. However, as noted above, in order for an artisan to know how to use a transgenic animal, that animal would have to express a phenotype. For example, an animal expressing an anti-tat ribozyme would have to express high enough levels of the ribozyme to elicit a protective effect after challenge with HIV. For the reasons discussed above, it is unpredictable whether a transgenic animal generated with a MAC would express a transgene, or whether the degree of expression would be sufficient to generate a phenotype in the animal. Because the specification does not disclose the generation of any transgenic animal by using a MAC, and in particular does not disclose the phenotype of such an animal, it is not enabling for how to make and use any transgenic animal by this method.

With regard to the ribozyme transgene, the specification teaches the generation of only one ribozyme (ribozyme D), and it would be predictable whether any other ribozyme would interfere with HIV expression *in vivo*. Given the large number of possible anti HIV ribozymes, an artisan would need to exercise undue experimentation in order to determine which ribozyme would function in an *in vivo* assay. It is noted that the courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. *Ex parte Maizel,* 27 USPQ2d 1662 (BPAI 1992).

Also, there is no disclosure in the art of transgenic reptiles or arachnids, as recited in claim 40, and the specification does not teach how to generate such animals. Therefore, the claims to transgenic reptiles or arachnids are not enabled.

Accordingly, it is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Furthermore, case law has established that in terms of predictability, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof, In re Marzocchi , 439 F.2d 220, 223 - 24, 169 USPQ 367, 368 - 70 (CCPA 1971).

Therefore, in view of the quantity of experimentation necessary to produce transgenic animals having viable MACs and properly expressing transgenes of interest, the lack of direction

and/or guidance provided by the specification demonstrating ES cell technology was established for any animal species other than mouse, the absence of working examples for the demonstration or correlation to making and using transgenic animals of all species, including mice, comprising MACs and expressing heterologous genes, and the unpredictable state of the art with regard to transgene behavior across species, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention without a reasonable expectation of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-44, 59, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32 and 43 are incomplete as written. The preamble of each method recites "for producing a transgenic animal". However, in claim 32, the only step of the method is the introduction of a SATAC into an embryonic cell which is not complete and consistent with the preamble. Even so, it is a big leap to go from manipulation of an embryonic stem cell to production of a transgenic animal. Likewise, in claim 43, the final step requires only the introduction of the minichromosome into an animal cell which is not complete and consistent with

the preamble. Amendment to the claims is requested. Note that claims 33-42 depend from claim 32, and claims 44, 59, and 60 depend from claim 43.

Claim 36 is unclear because there is no antecedent basis for "the product" in claim 32. It appears that the claim actually depends from claim 35. In the interest of compact prosecution, claim 36 has been examined on the assumption of dependency from claim 35.

Claim 37 is unclear because there is no antecedent basis for "the anti-HIV ribozyme" in claim 32. It appears that the claim actually depends from claim 36. In the interest of compact prosecution, claim 37 has been examined on the assumption of dependency from claim 36.

Claim 39 is unclear because there is no antecedent basis for "the product" in claim 32. It appears that the claim actually depends from claim 35. In the interest of compact prosecution, claim 39 has been examined on the assumption of dependency from claim 35. Claim 39 is also vague and indefinite in the recitation of "a plurality of antigens" and "a plurality of pathogens" because it is not clear how many antigens or pathogens are encompassed by the claim; the metes and bounds of the claim are not defined.

Claim 40 is vague and indefinite in the recitation of "the transgenic animal is a ... amphibians." The plural form of amphibian should be replaced by the singular "amphibian."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 42 is rejected under 35 U.S.C. 102(b) as being anticipated by Larsson *et al* (1994) (JQ).

Claim 42 is a product-by-process claim directed to a transgenic animal. Note that it is only the product which is anticipated by the prior art and not the process by which the product is made. This is because the final product (the transgenic animal) is not distinguished by any particular features or characteristics as a result of the process by which it is made. As such, the limitations of the transgenic animal of claim 42 are met by any transgenic animal in the prior art.

Larsson *et al.* teach a transgenic mouse harboring a ribozyme transgene directed against mouse β2M mRNA (see e.g. Abstract). As written, the claims do not require the expression of a transgene and do not recite a phenotype that would distinguish the claimed animal from any other transgenic animal. Therefore, the claimed animal is anticipated by the mouse taught by Larsson *et al.*

Inclusion in the claim of a cause-effect relationship between the transgene and the phenotype would obviate this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over either WO95/32297 (1995) (DV) (Brown *et al*) or Farr *et al* (1995) (GQ), either of the preceding in view of Brown *et al* (1992) (ED).

Claim 43 is drawn to a method for producing a transgenic animal comprising steps of: (1) introducing into a cell a DNA fragment comprising a selectable marker; (2) growing the cell under selective conditions that result in incorporation of the DNA fragment into the genomic DNA; (3) selecting a cell that comprises a minichromosome that is "about" 10 Mb to 50 Mb; and (4) isolating the minichromosome and introducing it into an animal cell.

Please note that the recitation "for producing a transgenic animal" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process, and where the

body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). As such, the claimed method is examined only on the basis of the recited steps which only require introduction of the minichromosomes into an animal cell.

Brown *et al.* (DV) and Farr *et al.* each disclose a method to produce an artificial minichromosome; in Brown *et al.* (DV), the source of the minichromosome is the human Y chromosome, whereas in Farr *et al.* the source is the human X chromosome. The methods comprise steps (1) - (3) as noted above, and produce minichromosomes of~8 Mb, a size encompassed by the claim of "about" 10-50 Mb (see e.g. p. 4, lines 1-28 of Brown *et al.* (DV), and Fig. 1 of Farr *et al.*). Brown *et al* (DV) and Farr *et al* differ from the claimed invention in that they do not explicitly teach isolating the minichromosome and introducing it into an animal cell.

However, at the time the invention was made, Brown *et al* (ED) had taught that artificial minichromosomes (MACs) could allow novel developmental or metabolic pathways to be introduced genetically into cells (see e.g. paragraph bridging pages 479 and 480). Therefore, it would have been obvious for a person of ordinary skill in the art at the time of the invention to use the minichromosome taught by either Brown *et al* (DV) or Farr *et al* as the basis for generating cells comprising MACs, with a reasonable expectation of success that the

minichromosomes would enter the cells and replicate. One would have been motivated to do so in order to study e.g. chromosome replication and function.

Thus, the claimed invention as a whole would have been *prima facie* obvious, in the absence of evidence to the contrary.

Claims 43, 59, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat. No. 5,288,625 (1994) (BH) (Hadlaczky) in view of Brown *et al* (1992) (ED).

Claims 43, 59, and 60 are drawn to a method for producing a transgenic animal comprising steps of: (1) introducing into a cell a DNA fragment comprising a selectable marker; (2) growing the cell under selective conditions that result in incorporation of the DNA fragment into the genomic DNA; (3) selecting a cell which comprises a minichromosome that is "about" 10 Mb to 50 Mb; and (4) isolating the minichromosome and introducing it into an animal cell. Claim 59 recites that the minichromosome is that present in the cell line EC3/7C5; claim 60 recites that the minichromosome is the λ neo-chromosome in the cell line KE1 2/4.

Please note that the recitation "for producing a transgenic animal" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA

1951). As such, the claimed methods are examined only on the basis of the recited steps which only require introduction of the minichromosomes into an animal cell.

Hadlaczky discloses a method to produce minichromosomes comprising steps (1) - (3) as noted above; the method is identical to that taught in the instant application. Hadlaczky also discloses the generation of a minichromosome from the cell line EC3/7C5 and the generation of the λ neo- chromosome (see e.g. col. 3, line 65 to col. 4, line 29). Hadlaczky differs from the claimed invention in that it does not explicitly teach isolating the minichromosomes and introducing them into animal cells.

However, at the time the invention was made, Brown *et al* (ED) had taught that artificial minichromosomes (MACs) could allow novel developmental or metabolic pathways to be introduced genetically into cells (see e.g. paragraph bridging pages 479 and 480). Therefore, it would have been obvious for a person of ordinary skill in the art at the time of the invention to use the minichromosomes taught by Hadlaczky as the basis for generating cells comprising MACs, with a reasonable expectation of success that the minichromosomes would enter the cells and replicate. One would have been motivated to do so in order to study e.g. chromosome replication and function.

Thus, the claimed invention as a whole would have been *prima facie* obvious, in the absence of evidence to the contrary.

Conclusion

No claim is allowable.

Claims 32-41, and 44 are free of the prior art, because there was no disclosure or suggestion in the prior art that "SATACs" could be used to generate transgenic animals. However, these claims are subject to other rejections.

The submission of numerous references in the IDS filed June 9, 1999, Paper No. 6, is noted. However, it appears that many of the references are directed toward non-analogous art. The Applicant is invited to particularly point out any other references which may be either specifically analogous or definitely pertinent to the claimed invention. The patent Applicant has duty not just to disclose prior art references but to make disclosure in such a way as not to "bury" it within other disclosures of less relevant prior art. *Golden Valley Microwave Foods Inc. v. Weaver Popcorn Co. Inc.*, 24 USPQ2d 1801 (DCInd).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jill Martin whose telephone number is (703)305-2147.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian R. Stanton, can be reached at (703)308-2081.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-0196.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

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